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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 11/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/016,403	HOLLADAY, LESLIE A.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26 and 29-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26 and 29-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/17/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 26 and 29-43 are pending in the application.

[2] Applicant's amendment to the claims, filed 21 August 2006, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[3] Applicant's arguments filed on 21 August 2006 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[4] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Claim Rejections - 35 USC § 112, Second Paragraph

[5] Claims 26, 30-36, and 38-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "one glutamine residue at position 16, 30, 31, or 36" in claim 26 (claims 30-35 dependent therefrom) and the term "at least two glutamine residues at positions 16, 24, 30, 31, or 36" in claim 36 (claims 38-43 dependent therefrom) are relative terms which renders the claim indefinite as it is unclear as to what the recited residue position is being compared. It is suggested that applicant identify whether the recited positions are relative to the parent polypeptide or the synthetic analog.

Claim Rejections - 35 USC § 112, First Paragraph

[6] Claims 30, 34-35, 38, and 42-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

MPEP § 2163 states, "when filing an amendment an applicant should show support in the original disclosure for new or amended claims" (MPEP 8th Ed., October 2006 Revision at pp. 2100-176 and 2100-183).and "[i]f the originally filed disclosure does not provide support for each claim limitation, or if an element which applicant describes as essential or critical is not claimed, a new or amended claim must be rejected under 35 U.S.C. 112, para. 1, as lacking adequate written description".

Claims 30 and 38 recite "hydrophobicity...increased," wherein applicant points to p. 8, lines 21-24 as showing support for this limitation. However, while the specification at p. 8, lines 21-24 supports an analog with "increased hydropholicity," it fails to support an analog with increased hydrophobicity as recited in the claims.

Claims 34-35 and 42-43 recite the limitation "anionic donor reservoir formulation...having a pH in the range of about 3.5 to about 7.4" (claims 34 and 42) or recite the limitation "the formulation...has a pH in the range of about 5 to about 7.4." Applicant points to p. 8, line 27 to p. 9, line 5 as showing support for these limitations.

While the specification at pp. 8-9 supports an anionic donor reservoir formulation having a pH in the range of 3.5 to 8, or 5 to 6, the specification fails to support the recited range of about 3.5 to about 7.4 or about 5 to about 7.4.

Applicant is invited to show support for the recited limitations at issue.

[7] Claims 26 and 29-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Initially, it is noted that MPEP 2111.01 states that "[d]uring examination, the claims must be interpreted as broadly as their terms reasonably allow." The limitations of parts (a) of claims 26 and 36 are product-by-process limitations. According to MPEP 2113, "'[e]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.'" As such, the only structural requirement of the synthetic analog is that it has at least one His (claim 26) or two His residues (claim 36). The claims do not preclude mutation of any other residue of h-GHRH, which, as noted in prior Office actions, is limited to SEQ ID NO:8. While applicant may argue that the analog is required to have a Gln replaced with His at the specified positions, however, as steps (a) of claims 26 and 36 are product-by-

process limitations, this is not required. Further, as there is no indication in steps (a) of 26 and 36 as to whether the recited positions are of the parent or analog, one can interpret the claim as meaning that the position(s) of the parent are altered, however, this does not preclude addition or deletion of amino acid residues following mutation of Gln of the parent GHRH to His, such that the resulting analog, while it is required to have one or more His residues, may not necessarily have the one or more His at its position(s) 16, 24, 30, 31, and/or 36. While it is acknowledged that the analog of claims 29 and 37 indicates that the positions are of the analog, the only structural requirement of the analog of claim 29 is that it have a His at positions 31 and 36 or the analog of claim 37 is that it have a His at positions 16, 24, 30, and 31, with any other sequence. It is also noted that, with the exception of claims 31 and 39, there is no functional requirement of the synthetic analog, such that the claim encompasses synthetic analogs with any biological activity.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus.

Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses only the following representative species of synthetic analogs of h-GHRH, *i.e.*, the polypeptide of SEQ ID NO:8, except Gln at position 16, 24, 30, 31, and/or 36, is replaced with His. The specification fails to describe any additional representative species of the claimed genus of nucleic acids. In the instant case, the recited genus of synthetic analogs encompasses species that are widely variant in both structure and function – as noted above. As such, the disclosure of the representative species of the polypeptide of SEQ ID NO:8, except Gln at position 16, 24, 30, 31, and/or 36, is replaced with His, is insufficient to be representative of the attributes and features of all species encompassed by the claimed genus of proteins.

Given the lack of description of a representative number of polynucleotides, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[8] Claims 26 and 29-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method using the polypeptide of SEQ ID NO:8, except Gln at position 16, 24, 30, 31, and/or 36, is replaced with His and wherein the polypeptide has GHRH activity, does not reasonably provide enablement for a method using any synthetic analog of GHRH as encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make and/or use the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: The limitations of parts (a) of claims 26 and 36 are product-by-process limitations. According to MPEP 2113, "'[e]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.'" As such, the only structural requirement of the synthetic analog is that it has at least one His (claim 26) or two His residues (claim 36). The claims do not preclude mutation of any other residue of h-GHRH, which, as noted in prior Office actions, is limited to SEQ ID NO:8. While applicant may argue that

the analog is required to have a Gln replaced with His at the specified positions, however, as steps (a) are product-by-process limitations, this is not required. Further, as there is no indication as to whether the recited positions are of the parent or analog, one can interpret the claim as meaning that the position(s) of the parent are altered, however, this does not preclude addition or deletion of amino acid residues following mutation of Gln of the parent GHRH to His, such that the resulting analog, while it is required to have one or more His residues, may not necessarily have the one or more His at its position(s) 16, 24, 30, 31, and/or 36. While it is acknowledged that the analog of claims 29 and 37 indicates that the positions are of the analog, the only structural requirement of the analog of claim 29 is that it have a His at positions 31 and 36 or the analog of claim 37 is that it have a His at positions 16, 24, 30, and 31, with any other sequence. It is also noted that, with the exception of claims 31 and 39, there is no functional requirement of the synthetic analog, such that the claim encompasses synthetic analogs with any biological activity.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: As noted above, while the specification provides an expectation that replacing Gln at position 16, 24, 30, 31, and/or 36 of SEQ ID NO:8 would result in a polypeptide that maintains the GHRH activity of SEQ ID NO:8, the specification fails to provide an expectation that replacing any other amino acid of SEQ ID NO:8 as encompassed by the claims would maintain the GHRH activity of the resulting synthetic analog. As noted in prior Office actions and undisputed by applicant, the effects of altering the amino acid sequence of a polypeptide on its function, even a single amino

acid alteration, were highly unpredictable at the time of the invention (see "Introduction to Protein Structure," Branden and Tooze, Garland Publishing, Inc., New York, 1991, p. 247; cited in a prior Office action). The high level of unpredictability is further evidenced by the references of Colman (*Res Immun* 145:33-36; cited in a prior Office action) and Abaza et al. (*J Prot Chem* 11:433-444; cited in a prior Office action), which teach that single amino acid changes within the interface of an antigen-antibody complex or even outside of an antigenic site can abolish the interaction entirely (p. 33, bottom of Colman and p. 433, abstract, of Abaza et al.). In view of the cited teachings, a skilled artisan would have recognized that, at the time of the invention, one could not predict the resulting functional effect(s) of replacing Thr with His in a polypeptide. "[I]f one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art." See MPEP § 2164.03.

The amount of direction provided by the inventor and The existence of working examples: The specification discloses prophetic examples of mutant h-GHRH having mutation at positions 16, 24, 30, and 31 (p. 18, bottom) and the prior art reference of Vale et al. (cited in the prior Office action) discloses an active GHRH analog at position 24. However, the specification fails to provide guidance regarding alteration of any other amino acids of SEQ ID NO:8 with an expectation that the polypeptide will maintain a therapeutic activity, namely that of GHRH. Furthermore, the specification fails to provide guidance for altering the polypeptide of SEQ ID NO:8 to achieve other biological

activities, or fails to teach how one can achieve a therapeutic result with a biologically-inactive polypeptide, the polypeptides of which are encompassed by the claims.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of isolating or generating variants of a polypeptide were known in the art at the time of the invention, it was not routine in the art to screen – by an essentially trial and error process – for all polypeptide variants having a substantial number of modifications and having any biological activity as encompassed by the claims for those polypeptides having the desired activity/utility.

In view of the lack of guidance and working examples provided in the specification and the high level of unpredictability as evidenced by the prior art, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

[9] Claims 26, 34-36, and 42-43 are rejected under 35 U.S.C. 102(b) as being anticipated by Chien et al. (*J Pharm Sci* 78:376-383, 1989; cited in the IDS filed on 2/28/2002). The claims are drawn to methods for delivering a polypeptide through a body surface using a synthetic analog of h-GHRH, wherein, as noted in the prior Office action, h-GHRH is limited to SEQ ID NO:8. As noted above, the "synthetic analog" of the claims has been broadly, but reasonably construed as encompassing any polypeptide having at least one His at any position (claim 26) or having at least two His at any position (claim 36).

The reference of Chien et al. teaches methods for the administration of insulin by iontophoresis across hairless rat skin (see particularly pp. 378-380) using a donor solution at pH 3.7, 5.2, or 7.1 (p. 380, Table III). This anticipates claims 26, 34-36, and 42-43 as written.

Claim Rejections - 35 USC § 103

[10] Claims 26, 31-36, and 39-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kumar et al. (*Proc Intern Symp Control Rel Bioact Mater* 17:435-436, Controlled Release Society, Inc., 1990; cited in a prior Office action) in view of Sage et al. (US Patent 5,494,679; cited in the IDS filed on 2/28/2002), Vale et al. (US Patent 4,528,190; cited in a prior Office action), and Voet et al. ("Biochemistry," John Wiley and Sons, New York, 1990; cited in a prior Office action). Claim 26 is drawn to a method for delivering a pharmaceutical polypeptide agent through a body surface by providing a synthetic analog of human growth releasing hormone (h-GHRH) having at least one Gln

to His substitution and delivering the analog through the body surface by electrotransport.

The reference of Kumar et al. teaches a method of iontophoretic delivery of h-GHRH (referred to as growth releasing factor or GRF in the references of Kumar et al., Sage et al., and Vale et al.) in a hairless guinea pig. Kumar et al. teaches h-GHRH was delivered in a buffer at pH 5.8 (p. 435, left column, bottom). The reference of Kumar et al. does not teach a h-GHRH with one or more His residues as wild-type h-GHRH does not appear to comprise a His residue (see SEQ ID NO:8 of the instant specification).

Sage et al. teaches that iontophoretic delivery of a therapeutic peptide can be improved by the following: (1) using an analog of a peptide, wherein the analog has an altered isoelectric point outside the range of skin (column 3, lines 57-60), wherein the isoelectric point is modified by replacing a neutral amino acid with a positively charged amino acid (column 5, lines 23-25); (2) using a peptide having high water solubility (column 4, lines 7-13), wherein water solubility is enhanced by replacing a neutral amino acid with a positively charged amino acid (column 5, lines 53-57); and (3) using a peptide of minimal size that maintains biological activity (column 3, lines 61-62), specifically teaching that h-GHRH can be reduced from its native 44 amino acid size by deleting C-terminal residues and still maintain "high potency" (column 5, lines 3-16).

As noted above, the reference of Sage et al. teaches replacing a neutral amino acid residue with a positively charged residue. Although the reference Sage et al. does not specifically suggest replacing a neutral amino acid with *His,* motivation to practice iontophoresis using a peptide with a neutral amino acid replaced with His is provided by

the reference of Green et al., which teaches iontophoresis of Ala-X-Ala tripeptides where X is a neutral, negative, or positive (His) amino acid (p. 1121, abstract, top). Green et al. teaches that the iontophoretic enhancement of the Ala-His-Ala was greater than peptides with neutral amino acids at the X position (p. 1124, left column; p. 1126, right column; and comparison of Figure 5(a) to Figures 1, 3, 6, and 7).

The reference of Vale et al. teaches synthetic peptide analogs of GHRH, including a peptide analog of h-GHRH with a His residue (Example XXVI) and a peptide analog with two His residues (Examples III and XIII), wherein the analogs have smaller sizes as compared to the corresponding native human growth hormone releasing factor due to deletion of C-terminal residues. Vale et al. teaches the Example peptides are considered to be biologically active (column 15, lines 48-49), useful for therapeutic applications in humans (column 16, lines 36-39), and have "generally greater" potency than a corresponding unmodified GHRH peptide (column 15, lines 44-48).

Although the references of Kumar et al., Sage et al. and Vale et al. do not specifically disclose His is positive at pH 5-6, but isolelectric at pH 7.4, Voet et al. evidences this by teaching that at pH 6, the side chain of His is 50% charged and at the basic end of physiological pH, His is neutral (p. 64, left column).

Therefore, at the time of the invention it would have been obvious to one of ordinary skill in the art to combine the teachings of Kumar et al., Sage et al. and Vale et al. to practice the method of iontophoretic delivery of Kumar et al. using the Example peptides of Vale et al. One would have been motivated to use the Example peptides of Vale et al. in the method of Kumar et al. because the Example peptides III, XIII, and

XXVI of Vale et al. have all of the improvements suggested by Sage et al. in that it has a reduced size relative to native h-GHRH and has a neutral amino acid at position 24 – Gln – replaced with a positive amino acid – His – and additionally has the advantage of having greater potency as compared to a corresponding unmodified h-GHRH. One would have been further motivated to use the Example III, XIII, or XXVI peptide of Vale et al. because of the teachings of Green et al. that iontophoretic enhancement of an Ala-His-Ala peptide was greater than peptides with a neutral amino acid. One would have had a reasonable expectation of success for practicing the method of iontophoretic delivery according to Kumar et al. using the Example III, XIII, or XXVI peptide of Vale et al. because of the teachings of Kumar et al. and Vale et al. Therefore, claims 26, 30-36, 38-43, drawn to the method described above would have been obvious to one of ordinary skill in the art at the time of the invention.

Conclusion

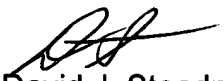
[11] Status of the claims:

- Claims 26 and 29-43 are pending.
- Claims 26 and 29-43 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Monday to Friday, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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Art Unit 1656